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Prevention of Invasive Pneumococcal Disease Among Black or African American Children With and Without Sickle Cell Disease in the United States After Introduction of 13-Valent Pneumococcal Conjugate Vaccine, 2005 Through 2019

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Abstract

Background: Administration of pneumococcal vaccines and oral penicillin prophylaxis has been recommended for children with sickle cell disease (SCD) to reduce the risk of invasive pneumococcal disease (IPD). Characterizing changes in IPD cases among children with SCD after 13-valent pneumococcal conjugate vaccine (PCV13) introduction could help inform the need for additional prevention measures.

Methods: Using data from Active Bacterial Core surveillance, we characterized IPD cases among Black or African American (Black) children aged less than 18 years with SCD, non-SCD IPD risk factors, and no IPD risk factors across three time periods (pre-PCV13 [2005–2009], early-PCV13 [2010–2014], and late-PCV13 [2015–2019]), and assessed proportion of IPD cases caused by serotypes in new pneumococcal conjugate vaccines (PCV15, PCV20) recommended after 2019. We analyzed IPD incidence among children with and without SCD.

Results: From 2005 to 2019, 1725 IPD cases were reported among Black children (6.9% with SCD). IPD incidence among children with SCD declined by 50% between pre-PCV13 and late-PCV13 periods (from 332 to 167 per 100,000), although IPD incidence among children with SCD was 42 times that of children without SCD in late-PCV13 period. During late-PCV13 period, greater than 95% of IPD cases among children with SCD were non-PCV13 serotypes; PCV15/non-PCV13 and PCV20/non-PCV15 serotypes caused 19% and 22% of cases, respectively. Increase in penicillin-nonsusceptible IPD cases was not observed.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Conclusions: Despite reductions in IPD incidence after PCV13 introduction, children with SCD are at increased risk of IPD compared to children without SCD. Use of higher valency PCVs may help reduce remaining IPD burden.

Keywords

13-valent pneumococcal conjugate vaccine; invasive pneumococcal disease; sickle cell disease

1 | Introduction

In the United States, approximately 100,000 people have sickle cell disease (SCD), a condition that increases the risk of invasive bacterial infections caused by encapsulated bacteria such as *Streptococcus pneumoniae* (*pneumococcus*) due to functional asplenia [1]. Invasive pneumococcal disease (IPD), such as pneumococcal bacteremia and meningitis, causes significant morbidity and mortality in children with SCD compared with children without SCD. To prevent IPD, the 2014 Evidence-Based Management of Sickle Cell Disease Expert Panel Report recommends that all children with SCD receive the recommended number of 13-valent pneumococcal conjugate vaccine (PCV13) doses followed by two doses of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) spaced 3 years apart [2]. In addition, oral penicillin prophylaxis is recommended through age 5 years unless a child had a splenectomy or IPD [2]. Understanding that the recommendations by the Advisory Committee on Immunization Practices (ACIP) may change over time, the panel recommended that children with SCD should follow the most up-to-date recommendation by the ACIP. With the approval of the new, 20-valent pneumococcal conjugate vaccine (PCV20) for children, in 2023, the ACIP recommended PCV20 as an option to complete the recommended pneumococcal vaccine series for children with certain underlying conditions who were previously recommended to receive PPSV23, including children with SCD [3].

Incidence of IPD among children with SCD in the United States dramatically declined after introduction of the 7-valent PCV (PCV7) in 2000, but remained higher than the incidence in the general pediatric population [4–6]. In the years prior to introduction of PCV13 in 2010, nearly a quarter of all IPD among children with SCD was caused by a serotype not covered in PCV7 but covered in PCV13; however, children with SCD had a smaller proportion of cases of IPD caused by serotypes covered in PCV13 compared with healthy children [4]. The assessment of PCV13 introduction among children with SCD in the United States is limited [7]. Most of those affected by SCD are of African ancestry or self-identify as Black [2], and in 2018–2019, Black children had approximately two times higher IPD rates compared with White children [8]. Therefore, we sought to characterize IPD cases and estimate incidence of IPD in Black or African American (Black) children with and without SCD before and after the introduction of PCV13. In addition, we estimated the proportion of IPD cases that were caused by serotypes contained in the new 15-valent and 20-valent PCVs (PCV15, PCV20) that were approved for use among US children in 2022 and 2023, respectively [3, 9].

2 | Materials and Methods

A case of IPD was defined as *S. pneumoniae* isolation or detection from a normally sterile site (e.g., blood or cerebrospinal fluid) among Black children less than age 18 years residing in Active Bacterial Core surveillance (ABCs) catchment areas during 2005–2019. ABCs is an active population- and laboratory-based surveillance system for invasive bacterial disease in the United States. ABCs catchment area expanded over time, and as of 2019, there were approximately 1.6 million Black children aged less than 18 years residing in the surveillance area [10]. Surveillance methods have been previously described [4, 11]. Briefly, ABCs collects demographic, hospitalization, outcome information, and relevant underlying conditions (including SCD) for all cases via medical chart review. All available pneumococcal isolates are tested for antibiotic susceptibility by the Clinical Laboratory and Standards Institute broth microdilution procedure (all isolates sent to the Minnesota Department of Health or isolates sent to CDC before 2015) or predicted by whole genome sequencing (2015–2019 for isolates sent to CDC). Serotyping is performed using Quellung reaction, polymerase chain reaction, or whole genome sequencing.

2.1 | Definitions

Antibiotic-nonsusceptible isolates were defined as those intermediate or fully resistant to one or more antibiotic classes according to 2019 Clinical and Laboratory Standards Institute breakpoints [11, 12]. For penicillin, we applied 2008 meningitis and nonmeningitis breakpoints for respective meningitis and nonmeningitis cases for the entire study period. Similarly, for tetracycline, we used pre-2013 breakpoints. Antibiotic classes included antifolates (trimethoprim-sulfamethoxazole), carbapenems (meropenem), cephalosporins (cefuroxime, ceftriaxone, or cefotaxime), fluoroquinolones (levofloxacin), glycopeptides (vancomycin), lincosamides (clindamycin), macrolides (erythromycin), oxazolidinones (linezolid), penicillins (penicillin or amoxicillin), and tetracyclines (tetracycline).

PCV13-type includes the 13 serotypes included in the vaccine (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), as well as serotype 6C, which is cross-reactive with the serotype 6A antigen in PCV13 and thus declined after PCV13 introduction [13]. The proportion of IPD cases caused by PCV13-type 3, 19A, and 19F were described separately, as these serotypes caused the majority of the remaining PCV13-type IPD in US children [14]. PCV15-type includes the 13 serotypes in PCV13 plus 22F and 33F. PCV20-type includes the 15 serotypes in PCV15 plus 8, 10A, 11A, 12F, and 15B. Isolates classified as serotype 15B/C were also included. PPSV23-unique-type includes 2, 9N, 17F, and 20. All other serotypes were considered non-vaccine serotypes (NVT).

2.2 | Statistical Analysis

Cases were grouped into three time periods: (i) Pre-PCV13 (2005–2009); (ii) Early-PCV13 (2010–2014); and (iii) Late-PCV13 (2015–2019). These time periods were chosen based on availability of data and to allow analysis of key demographics, risk factors, and outcomes, both immediately after PCV13 introduction and in the years immediately before the COVID-19 pandemic (a potential baseline for future analyses). Prevalence of SCD within the ABCs catchment area was estimated as previously described [4]. Incidence of

IPD in Black children with SCD was estimated by dividing the number of cases of IPD in Black children with SCD reported to ABCs in a given time period by the estimated number of Black children with SCD in the ABCs catchment area during that time period. The number of Black children with SCD in the ABCs catchment area was estimated by generating state-specific SCD prevalence estimates using a method similar to that of Hassel [15]. A sensitivity analysis assessed the impact of potentially overestimating or underestimating the number of children with SCD in the ABCs catchment area by varying the estimated population size from 50% of the estimate to 175% of the estimate. IPD rates and corresponding 95% confidence intervals were estimated using a Poisson regression model. Descriptive analyses compared IPD cases among children with SCD (regardless of the presence of other underlying conditions), children without SCD who had one or more risk factors for IPD (anatomic or functional asplenia, bone marrow transplant, cerebrospinal fluid leaks, chronic heart disease, chronic lung disease, chronic renal failure, complement deficiency, diabetes, hematologic malignancy, HIV-infection [excluding ABCs New York site where HIV status is not reportable], immunoglobulin deficiency, on immunosuppressive therapy, nephrotic syndrome, organ transplant, or solid cancer), and children without these risk factors. Comparisons were made using chi-square, Fisher's exact, *t*-tests and by examination of confidence intervals. Differences were considered statistically significant at $p < 0.05$ and/or if confidence intervals of the incidence rate ratios (IRR) did not overlap the null. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc.).

This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy (see e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

3 | Results

A total of 1725 cases of IPD occurred in Black children aged less than 18 years in the catchment area during 2005–2019 (Table 1). Of these, 119 (6.9%) had SCD identified during their medical chart review. An additional 355 (20.6%) had one or more IPD risk factor(s) without SCD. In all time periods, children with SCD and those with other risk factors were significantly older at the time of culture than children without IPD risk factors.

3.1 | Clinical Presentation and Outcomes

Children with SCD were more likely than either of the other groups to have bacteremia without focus during the pre-PCV13 and early-PCV13 time periods; however, this difference was not statistically significant in the late-PCV13 time period (Table 1). While children with SCD were significantly more likely than children without IPD risk factors to be hospitalized during their IPD episode during all time periods, median length of hospitalizations was similar among hospitalized children across all risk groups.

3.2 | Trends in IPD Incidence

Incidence of IPD among children aged less than 18 years with SCD declined 50% during the study period, from 332 per 100,000 children before PCV13 introduction to 167 per 100,000 children after vaccine introduction (Table 2). However, incidence of IPD among

children with SCD remained higher than the incidence among children without SCD. The IRR comparing the incidence of IPD among children with SCD and without (i.e., non-SCD risk factors and no risk factors) was 28 [21–37] in the pre-PCV13 period, 42 [30–57] in the early-PCV13 period, and 42 [29–62] in the late-PCV13 period. The remaining disparities in IPD incidence among children with SCD compared with those without were more pronounced in children aged ≥ 5 years (IRR range: 67–71) compared with children aged less than 5 years (IRR range: 17–32). A sensitivity analysis assessing the impact of potentially overestimating or underestimating the number of children with SCD in the ABCs catchment area indicated that increased IPD incidence in children with SCD was noted even in the most extreme assumptions of over- or underestimation of the number of children with SCD in the ABCs catchment area population (Table S1).

3.3 | Characteristics of IPD Cases

Significant declines in the proportion of PCV13-type IPD cases were seen amongst all the three groups after the introduction of PCV13 (Table 3). During all time periods, the proportion of children with SCD with IPD caused by one of the PCV13 serotypes was significantly smaller than the proportion seen in other groups. During the late-PCV13 period, only one PCV13-type IPD case was identified among children with SCD (due to serotype 19A), whereas PCV13-type IPD cases (primarily due to serotypes 3, 19A, and 19F) caused more than 27% of overall IPD cases in the non-SCD groups. Among children with SCD, additional serotypes contained in PCV15 (but not in PCV13) or PCV20 (but not in PCV15) caused 19% and 22% of IPD cases, respectively, and no IPD case was caused by one of the serotypes unique to PPSV23. Non-vaccine type caused 56% of IPD cases, and this proportion was significantly higher than the proportion seen in non-SCD groups.

In the early-PCV13 period, IPD isolates obtained from children with SCD were significantly more likely than children without IPD risk factors to be nonsusceptible to one or more class of antibiotics (60% of isolates in children with SCD vs. 45% in the no-risk-factors group). In children with SCD, these isolates comprised multiple pneumococcal serotypes (i.e., serotypes 15B, 15A, 35B, 23B), whereas in children with no IPD risk factors, serotype 19A was the most common (34.3%) serotype. No other significant differences in the proportion of isolates nonsusceptible to one or more class of antibiotics between groups or time periods were noted. There were no statistically significant differences in the proportion of IPD isolates nonsusceptible to parental or oral penicillin in children with SCD compared with those from other groups in any time period.

4 | Discussion

Our study showed that overall IPD incidence in Black children aged less than 18 years with SCD has dropped by 50% after PCV13 introduction, from 2005–2009 to 2015–2019. Despite the reduction, the IPD incidence continues to be dramatically higher than the incidence among Black children without SCD. A higher proportion of non-PCV13 serotypes among children with SCD compared to children without SCD could have contributed to these disparities. In the late-PCV13 period, greater than 95% of IPD cases among children with SCD were due to non-PCV13 serotypes; 41% were due to serotypes in PCV20, none

were due to PPSV23-unique serotypes, and slightly more than half were due to serotypes that are not contained in any of the existing pneumococcal vaccines.

The 2014 Evidence-Based Management of Sickle Cell Disease recommends that children with SCD receive timely administration of both PCV and PPSV23 and oral penicillin prophylaxis to prevent IPD [2]. PCVs induce T-cell dependent immune response, which allows a more robust immune response compared with PPSV23. In children, PPSV23 is only recommended for children aged ≥ 2 years with underlying conditions that increase the risk of IPD, as T-cell independent antibody response to PPSV23 is poor in younger children [16]. Therefore, children who are recommended to receive PPSV23 are recommended to receive both PCV and PPSV23, with PPSV23 providing additional serotype coverage not contained in PCV. In our study, additional serotypes included in PCV15 and PCV20 (but not in PCV13) caused 19% and 41% of IPD, respectively, among children with SCD in the late-PCV13 period. On the other hand, there was no IPD case caused by PPSV23-unique serotypes among children with SCD during the entire study period. This indicates that use of new PCVs that were recommended in recent years could further reduce IPD incidence in this population. However, still over 50% of IPD in children with SCD was caused by a non-vaccine serotype (NVT) in the late-PCV13 time period, pointing to the need for additional prevention measures such as oral penicillin prophylaxis and the development of vaccines with broader coverage. Importantly, the proportion of IPD cases nonsusceptible to penicillin did not increase over time. Continued IPD surveillance is important to monitor the impact of new vaccines and efforts to increase penicillin prophylaxis utilization.

Oral penicillin prophylaxis is known to be an effective way in protecting children with SCD from IPD and has been recommended for high-risk children for nearly four decades [17, 18]. Children with sickle cell anemia, the most severe form of SCD, are recommended to receive oral penicillin prophylaxis until age 5 years unless a child had splenectomy or had IPD [2]. While we were unable to assess adherence to penicillin prophylaxis among children with IPD in our study, studies have reported that adherence to antibiotic prophylaxis among children with SCD has been suboptimal [19, 20]. This suggests the importance of continued education and emphasis on oral penicillin prophylaxis for children with indications, along with receiving recommended pneumococcal vaccine doses. Additionally, consistent with previous reports [4, 7], children with SCD had an older age of onset of IPD compared with children without SCD, and 25% of children with SCD and IPD in our study were of age ≥ 5 years in all time periods. In general, IPD incidence decreases with increasing age in children; however, the older age of onset seen in children with SCD suggests that the reduction in IPD incidence in children with SCD is smaller compared with children without SCD, supported by the higher IRR among children aged 5–17 years compared with children aged less than 5 years. It is possible the older age of IPD onset among children with SCD is related to cessation of penicillin prophylaxis after age 5 years. A survey of pediatric hematologists indicated 76% routinely recommended cessation of penicillin prophylaxis after 5 years of age, with 27% of pediatric hematologists who recommend cessation of penicillin prophylaxis after 5 years of age citing concerns related to emergence of antibiotic resistance as a reason for their recommendation [21]. In our study, there were no statistically significant differences in the proportion of IPD isolates nonsusceptible to parental or oral penicillin in children with SCD compared with those from other groups in any time period.

However, the possibility of unintended consequences, such as development of resistance against non-pneumococcal pathogens or disruption of microbiome, cannot be ruled out [22]. Furthermore, for children who have not received PCV20, ACIP currently [3] recommends a second dose of PPSV23 after 5 years of the first dose, instead of 3 years as recommended by the Expert Panel Report [2]. Further research may be needed to identify the most appropriate age to cease penicillin prophylaxis and vaccination schedules for children with SCD.

Our study is subject to a few limitations. First, because the number of children living with SCD was not known, we estimated rates of SCD in the ABCs catchment area to define the SCD population. It is possible these estimates either over- or underestimated the total number of children with SCD in the surveillance catchment area. However, sensitivity analyses showed even in the most extreme assumptions of over- or underestimation of the number of children with SCD in the ABCs catchment area population, children with SCD continued to have a significantly higher incidence rate compared with children without SCD, with higher IRR among children aged 5–17 years than children aged less than 5 years. Second, we were unable to characterize the risk profile of IPD cases among children with SCD by SCD type. Third, we were unable to capture receipt of preventive measures (e.g., pneumococcal vaccination, penicillin prophylaxis, hydroxyurea utilization), limiting our ability to attribute noted differences between groups to differences in receipt of preventive measures or potential waning effectiveness of these preventive measures over time. Fourth, differences in case ascertainment efforts among children with and without SCD could have potentially overestimated the IRR between the two groups. In children with no IPD risk factors, the proportion of hospitalized children was lower compared with children with SCD during the study period, although the proportion increased over time. It has been reported that obtaining blood cultures from children with no IPD risk factors has become less common since PCV introduction, especially in the outpatient setting, as detection of *S. pneumoniae* from cultures obtained from otherwise healthy children has become rare [23]. On the other hand, national guidelines recommend febrile patients with SCD should be hospitalized and closely monitored whenever infection is suspected [2], making it potentially more likely for IPD cases to be detected and hospitalized in children with SCD compared with children without SCD. Fifth, as HIV status is not reportable in ABCs New York site, we could have underestimated the number of IPD cases among children with other IPD risk factors; however, IPD cases among children with HIV have been less common compared with non-HIV risk factors, so the degree of underestimation is expected to be small. Lastly, given the small number of IPD cases among children with SCD in the late-PCV13 period, certain estimates (e.g., serotype distribution) may have been unreliable.

5 | Conclusion

This report demonstrates that introduction of PCV13 reduced the incidence of IPD in children with and without SCD, primarily due to reduction in PCV13-type IPD cases. However, our analyses show children with SCD are still at much greater risk of IPD infection than healthy children, pointing to the need for better prevention strategies to reduce the overall morbidity due to IPD in children with SCD. Use of new PCVs may help prevent additional disease burden in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from Active Bacterial Core Surveillance Team. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Active Bacterial Core Surveillance Team.

Abbreviations:

ABCs Active Bacterial Core surveillance

ACIP	Advisory Committee on Immunization Practices
IPD	invasive pneumococcal disease
IRR	incidence rate ratio
NVT	non-vaccine serotypes
PCV13	13-valent pneumococcal conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
SCD	sickle cell disease

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TABLE 1 |
Characteristics of Black or African American children aged younger than 18 years with IPD by time period, 2005–2019.

	Pre PCV13 (2005–2009)				Early PCV13 (2010–2014)				Late PCV13 (2015–2019)			
	SCD ^a (N = 48)	Other IPD risk factors ^b (N = 160)	No IPD risk factors (N = 668)	SCD (N = 42)	Other IPD risk factors ^b (N = 107)	No IPD risk factors (N = 359)	SCD ^c (N = 29)	Other IPD risk factors ^b (N = 88)	No IPD risk factors (N = 224)			
Average cases/year	9.6	32	133.6	8.4	21.4	71.8	5.8	17.6	44.8			
Age in months, median (IQR: Q1–Q3)	46 (23–75)	41 (21–86)	18 (9–40)	41 (20–74)	51 (24–85)	21 (11–41)	49 (19–79)	56 (29–106)	20 (10–56)			
Clinical ^d , n (%)												
Bacteremia without focus	30 (62.5)	60 (37.5)	294 (44.0)	28 (66.7)	44 (41.1)	144 (40.1)	14 (48.3)	28 (31.8)	83 (37.1)			
Bacteremic pneumonia	15 (31.3)	82 (51.3)	253 (37.9)	6 (14.3)	41 (38.3)	123 (34.3)	9 (31.0)	33 (37.5)	87 (38.8)			
Meningitis	2 (4.2)	5 (3.1)	47 (7.0)	4 (9.5)	7 (6.5)	34 (9.5)	1 (3.4)	9 (10.2)	30 (13.4)			
Other	2 (4.2)	13 (8.1)	80 (12.0)	4 (9.5)	16 (15.0)	58 (16.2)	5 (17.2)	18 (20.5)	27 (12.1)			
Hospitalized, n (%)	45 (93.8)	114 (71.3)	365 (54.9)	40 (95.2)	85 (79.4)	234 (65.5)	28 (96.6)	79 (89.8)	167 (74.9)			
Length of hospitalization in days, median (Q1–Q3)	4 (3–6)	5 (3–12)	5 (3–10)	5 (4–7)	5 (3–10)	5 (3–10)	5 (3–12)	5 (3–11)	4 (3–10)			
Died, n (%)	4 (8.3)	3 (1.9)	5 (0.7)	0 (0.0)	2 (1.9)	8 (2.2)	3 (10.3)	3 (3.4)	12 (5.4)			

Abbreviations: IPD, invasive pneumococcal disease; IQR, interquartile range; PCV13, 13-valent pneumococcal conjugate vaccine; SCD, sickle cell disease.

^a N = 1 child with SCD had received a bone marrow transplant.

^b Children without SCD who had ≥1 risk factor for IPD (anatomic or functional asplenia, bone marrow transplant, cerebrospinal fluid leaks, chronic heart disease, chronic lung disease, chronic renal failure, complement deficiency, diabetes, hematologic malignancy, HIV-infection [excluding ABCs New York site where HIV status is not reportable], immunoglobulin deficiency, on immunosuppressive therapy, nephrotic syndrome, organ transplant, or solid cancer).

^c N = 1 child with SCD had received a bone marrow transplant.

^d Some with meningitis may also have bacteremic pneumonia.

TABLE 2 |
Incidence of IPD among children with SCD compared to children without SCD by age group and time period, 2005–2019.

	Pre PCV13 (2005–2009)			Early PCV13 (2010–2014)			Late PCV13 (2015–2019)		
	SCD (Cases per 100,000)	No SCD (Cases per 100,000)	IRR (95% CI)	SCD (Cases per 100,000)	No SCD (Cases per 100,000)	IRR (95% CI)	SCD (Cases per 100,000)	No SCD (Cases per 100,000)	IRR (95% CI)
0–17 years	332	12	28 (21–37)	256	6	42 (30–57)	167	4	42 (29–62)
0–4 years	568	33	17 (12–25)	551	17	32 (22–47)	297	10	29 (17–49)
5–17 years	210	3	67 (42–107)	124	2	70 (40–123)	114	2	71 (40–124)

Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; IRR, incidence rate ratio; PCV13, 13-valent pneumococcal conjugate vaccine; SCD, sickle cell disease.

TABLE 3 |

Characteristics of serotypes identified in Black or African American children younger than 18 years old with IPD by time period, 2005–2019.

	Pre PCV13 (2005–2009)				Early PCV13 (2010–2014)				Late PCV13 (2015–2019)			
	SCD (N = 48)	Other IPD risk factors (N = 160)	No IPD risk factors (N = 668)	SCD (N = 42)	Other IPD risk factors (N = 107)	No IPD risk factors (N = 359)	SCD (N = 29)	Other IPD risk factors (N = 88)	No IPD risk factors (N = 224)			
Serotype ^a , n (%)												
PCV13 serotypes ^b	19 (47.5)	96 (67.1)	364 (62.3)	5 (12.5)	38 (38.0)	121 (37.7)	1 (3.7)	21 (27.3)	52 (27.5)			
3	0 (-)	4 (2.8)	24 (4.1)	0 (-)	2 (2.0)	8 (2.5)	0 (-)	7 (9.1)	18 (9.5)			
19F	0 (-)	5 (3.5)	5 (0.9)	0 (-)	0 (0.0)	6 (1.9)	0 (-)	2 (2.6)	18 (9.5)			
19A	8 (20.0)	60 (42.0)	252 (43.2)	1 (2.5)	26 (26.0)	75 (23.4)	1 (3.7)	5 (6.5)	15 (7.9)			
PCV15-unique serotypes ^c	3 (7.5)	9 (6.3)	57 (9.8)	2 (5.0)	14 (14.0)	56 (17.4)	5 (18.5)	6 (7.8)	25 (13.2)			
PCV20-unique serotypes ^d	3 (7.5)	10 (7.0)	42 (7.2)	10 (25.0)	16 (16.0)	51 (15.9)	6 (22.2)	10 (13.0)	24 (12.7)			
PPSV23-unique serotypes ^e	0 (-)	6 (4.2)	7 (1.2)	0 (0.0)	1 (1.0)	9 (2.8)	0 (-)	2 (2.6)	5 (2.6)			
Non-vaccine serotypes	15 (37.5)	22 (15.4)	114 (19.5)	23 (57.5)	31 (31.0)	84 (26.2)	15 (55.6)	38 (49.4)	83 (43.9)			
Nonsusceptible to ≥1 class of antibiotics ^f , n (%)	18 (45.0)	65 (45.5)	243 (41.5)	24 (60.0)	48 (48.5)	143 (44.8)	15 (55.6)	35 (45.5)	88 (46.8)			
Nonsusceptible to penicillin ^g , n (%)												
Breakpoint for parental penicillin	5 (12.5)	25 (17.5)	101 (17.2)	5 (12.5)	14 (14.1)	49 (15.4)	0 (-)	5 (6.5)	14 (7.4)			
Breakpoint for oral penicillin	23 (57.5)	59 (41.3)	241 (41.1)	17 (42.5)	36 (36.4)	114 (35.8)	11 (40.7)	32 (41.6)	59 (31.2)			

Abbreviations: IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

^aSerotype data were missing from some of the cases; % is based on isolates with serotype information.

^bPCV13 types include all serotypes in the 13-valent pneumococcal conjugate vaccine, plus serotype 6C due to cross-reactivity with vaccine type 6A.

^cSerotypes 22F and 33F, which are not included in PCV13.

^dSerotypes 8, 10A, 11A, 12F, or 15B that are included in PCV20 but not in PCV15. During 2010–2013, a total of 7 cases that had 15B/C are included in this group (2 in those with SCD, 3 in those with other risk factors, and 2 in those with no IPD risk factors).

^eSerotypes 2, 9N, 17F, and 20.

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Antibiotic-susceptible isolate defined as an isolate that was intermediate or resistant to ≥ 1 antibiotic in the following antibiotic classes: antifolates (trimethoprim-sulfamethoxazole), carbapenems (meropenem), cephalosporins (cefuroxime, ceftriaxone, or cefotaxime), fluoroquinolones (levofloxacin), glycopeptides (vancomycin), lincosamides (clindamycin), macrolides (erythromycin), oxazolidinones (linezolid), penicillins (penicillin or amoxicillin), or tetracyclines (tetracycline); % is based on isolates with antibiotic susceptibility data available.

^fIncludes resistant and intermediate susceptibility to penicillin; % is based on isolates with antibiotic susceptibility data available.